

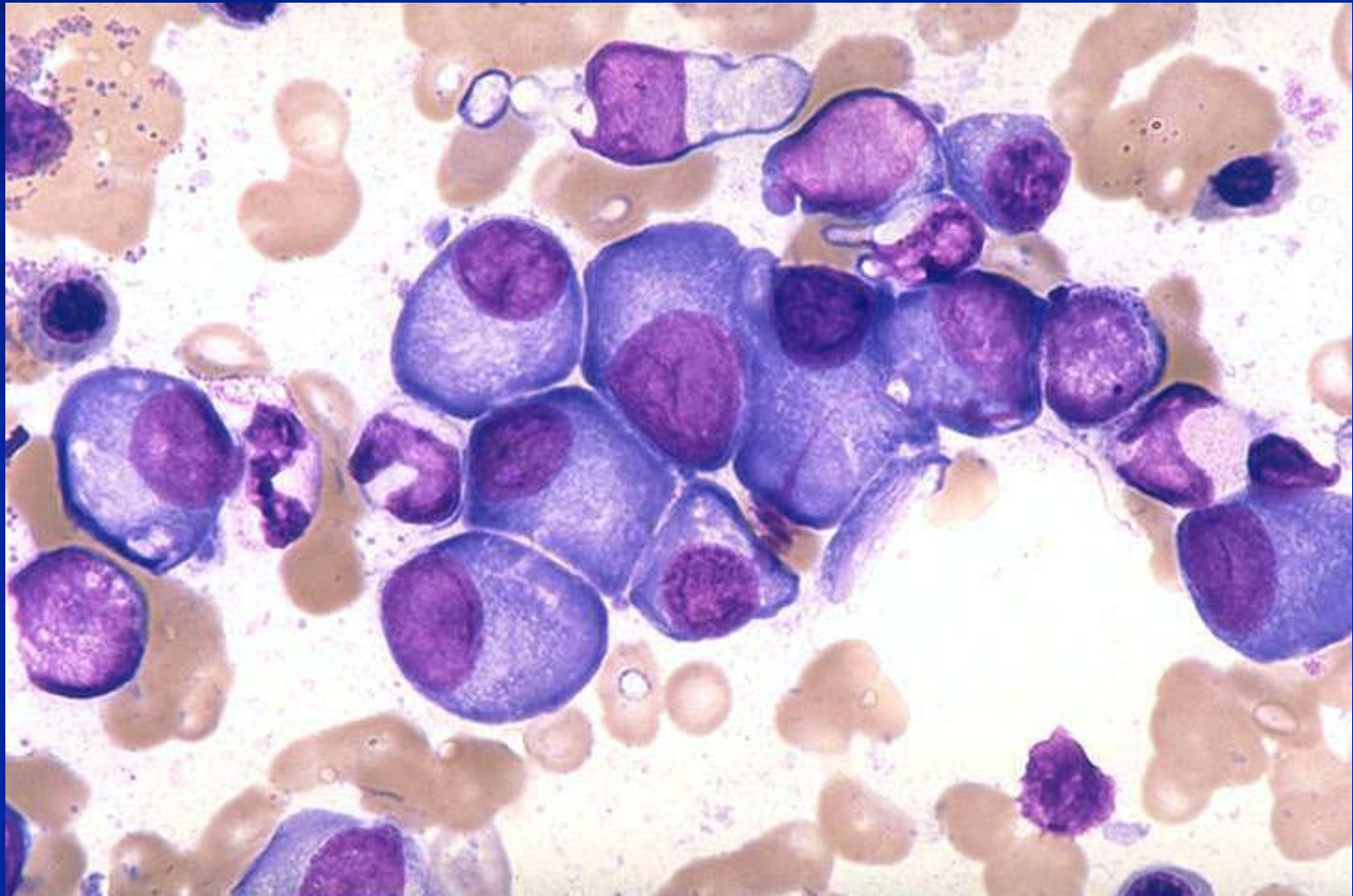
Epoetin Alfa Induces Tumor Regression and Antitumor Immune Responses in Myeloma Patients and in a Murine Myeloma Model

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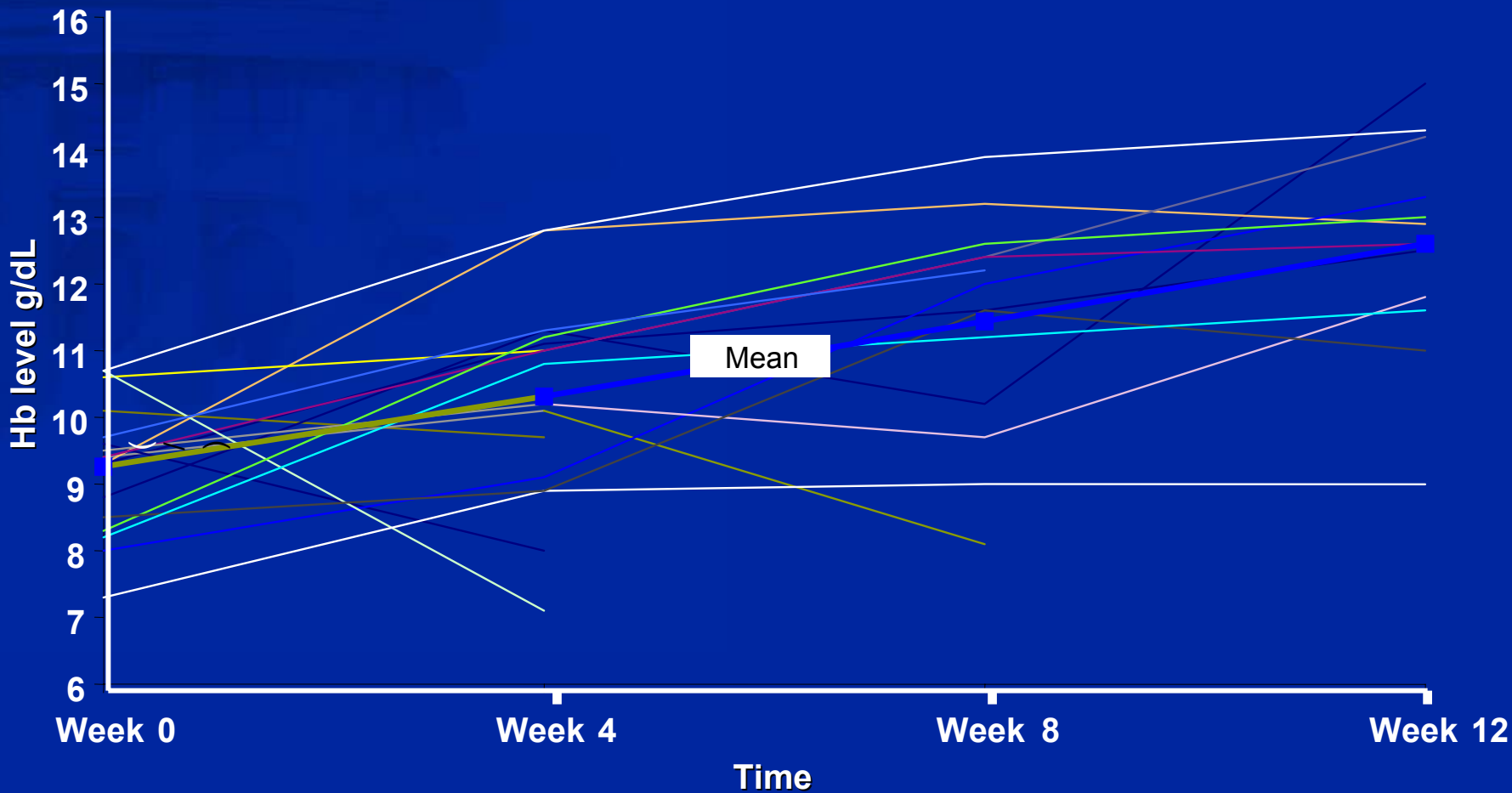


AVENNA

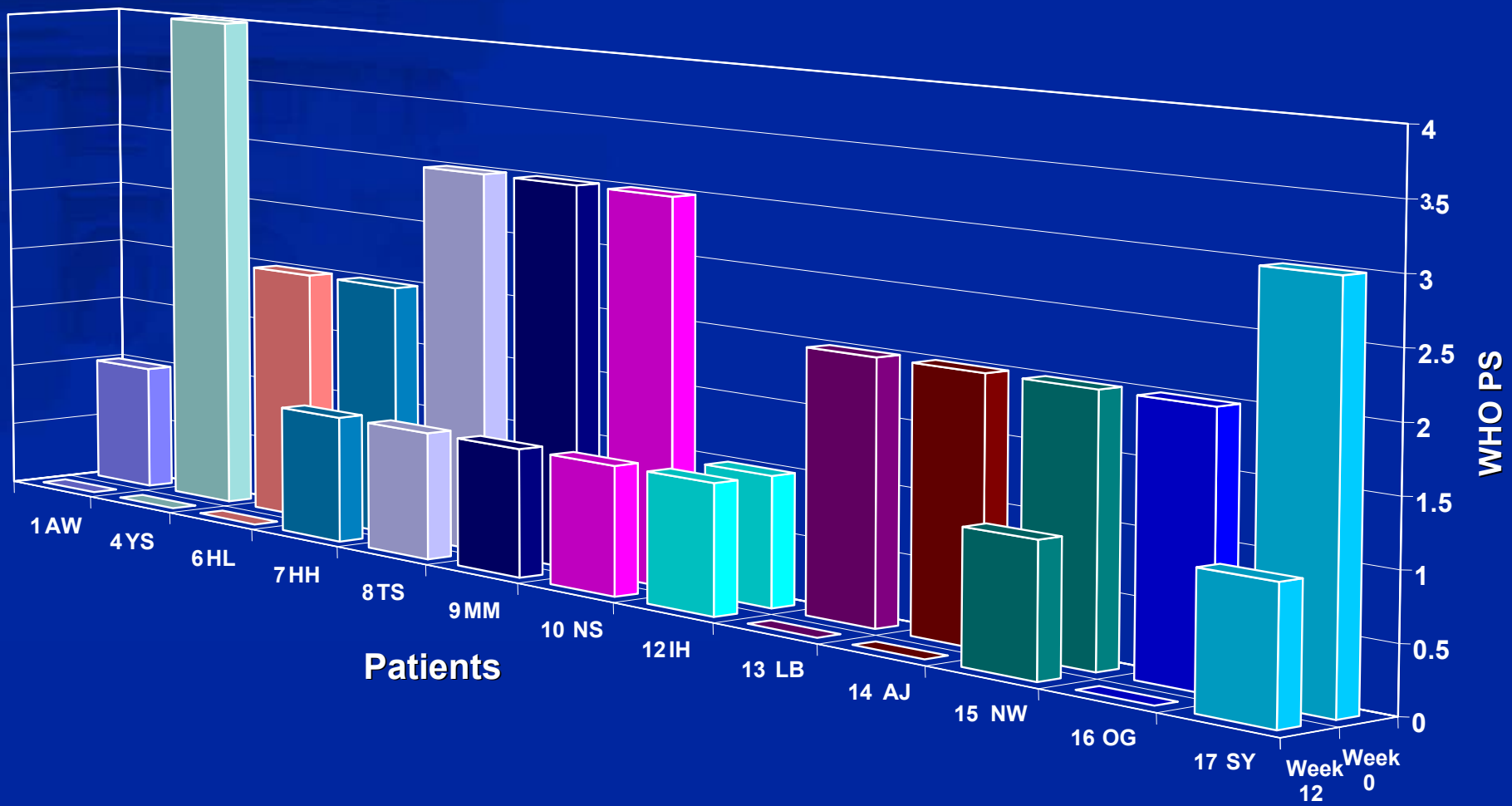
Multiple Myeloma (MM) Cells



Epoetin Alfa Affects Hb Levels in MM (n = 13)



Improvement in WHO Score in Epoetin Alfa-Treated Patients ($n = 13$)



Patient OG

- **1/95: Presentation**
 - 44 years, female, weakness, weight loss
 - Physical examination: looks sick, pale
 - Lab: Hb 8 g/dL, TP 13, Glob 10, IgG-K, 90% PC
 - Diagnosis: multiple myeloma (stage III)
 - Rx: VMCP-VBAP, VAD, HDC
- **8/95: Disease progression**
 - Hb 8.5 g/dL; treatment (Tx) 3; PS 2-3; began epoetin alfa
- **10/95: Hb 12 g/dL; Tx 0; PS 0; TP 15**
- **3/03: Patient active, on epoetin alfa + clodronate; 7.5 years**

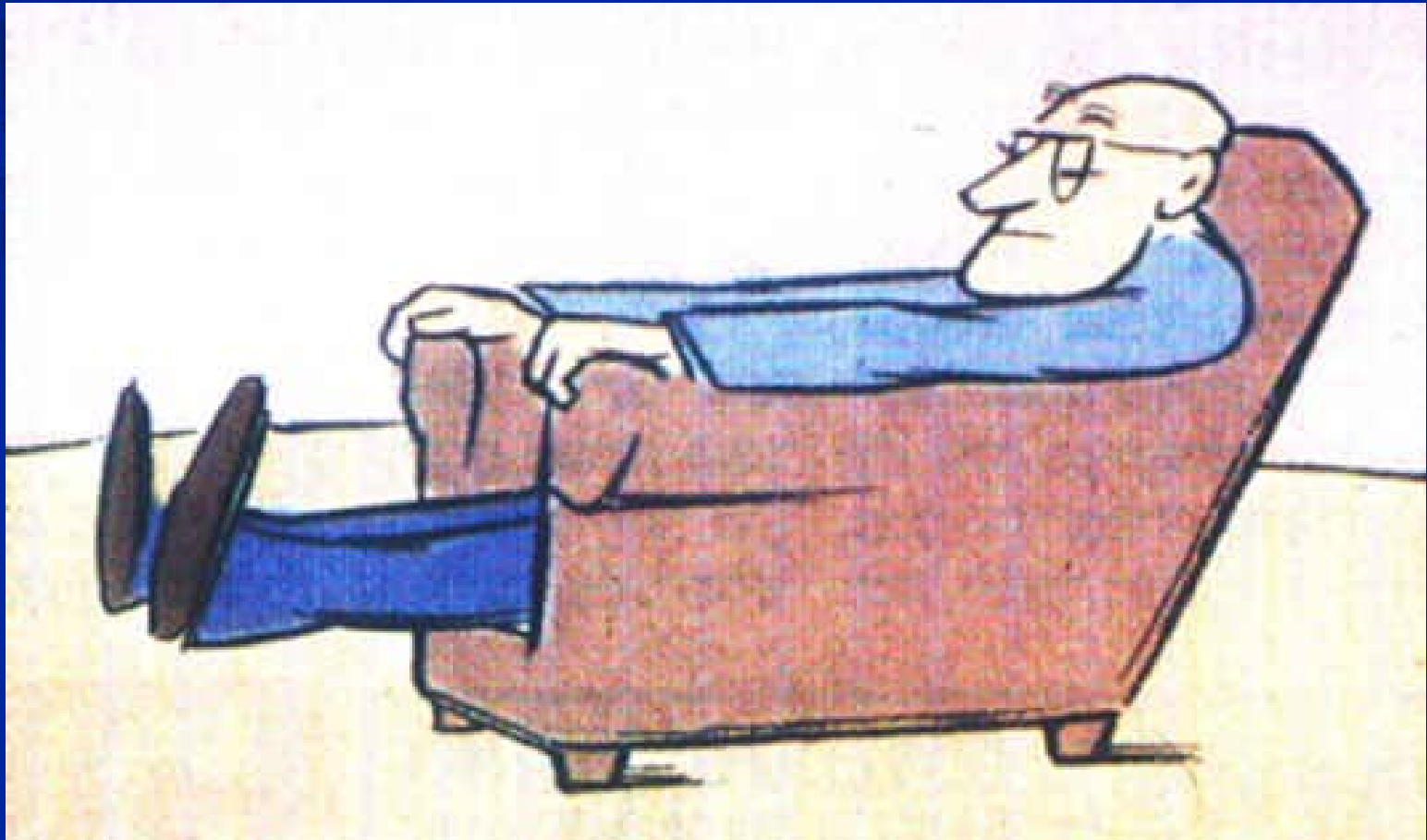


Long-Term Epoetin Alfa Treatment in Poor Prognosis MM Patients

Patient	Age/ sex	MM type	Poor prognostic	Other Rx for MM	Total epoetin Rx mo (yr)	Comments
JS	59 M	LC-I	RF, CHF Amyloid	MP	79 (6.5)	Dialysis; MI
OG	44 F	IgG-k	Very high tumor mass	Many	82+ (~7)*	M-spike >10 g/dL
LB	68 F	IgG-k	High Ca	MP, RT	68 (6)	Breast Ca
TS	73 F	IgG-l	RF, HT, Amyloid	MP Plasma	43 (3.5)	MDS
MB	55 M	IgG-l	Very high tumor mass	Many	44 (3.5)	Numerous lytic lesions

*Relatively stable at 20.3.03

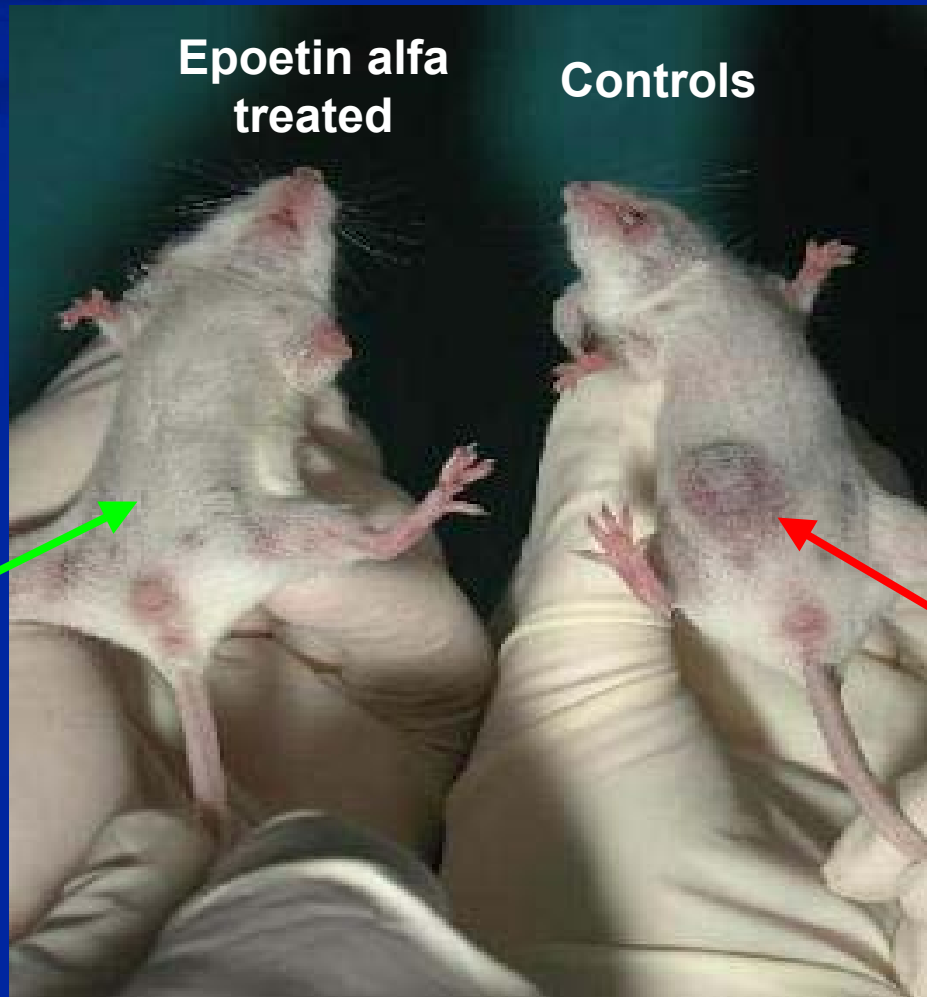
Let's Think...



Mouse Model: Epoetin Alfa in MM

- 10^4 MOPC-315 cells sc into BALB/c
- Local abdominal tumor on day 11-13
- Monoclonal protein: IGA-L (27 Kd)
- Course: tumor progresses (90%), death 40-50 d
- Intervention: epoetin alfa (30 IU) when tumor palpable
- End points: progression/regression, tumor, M protein, survival

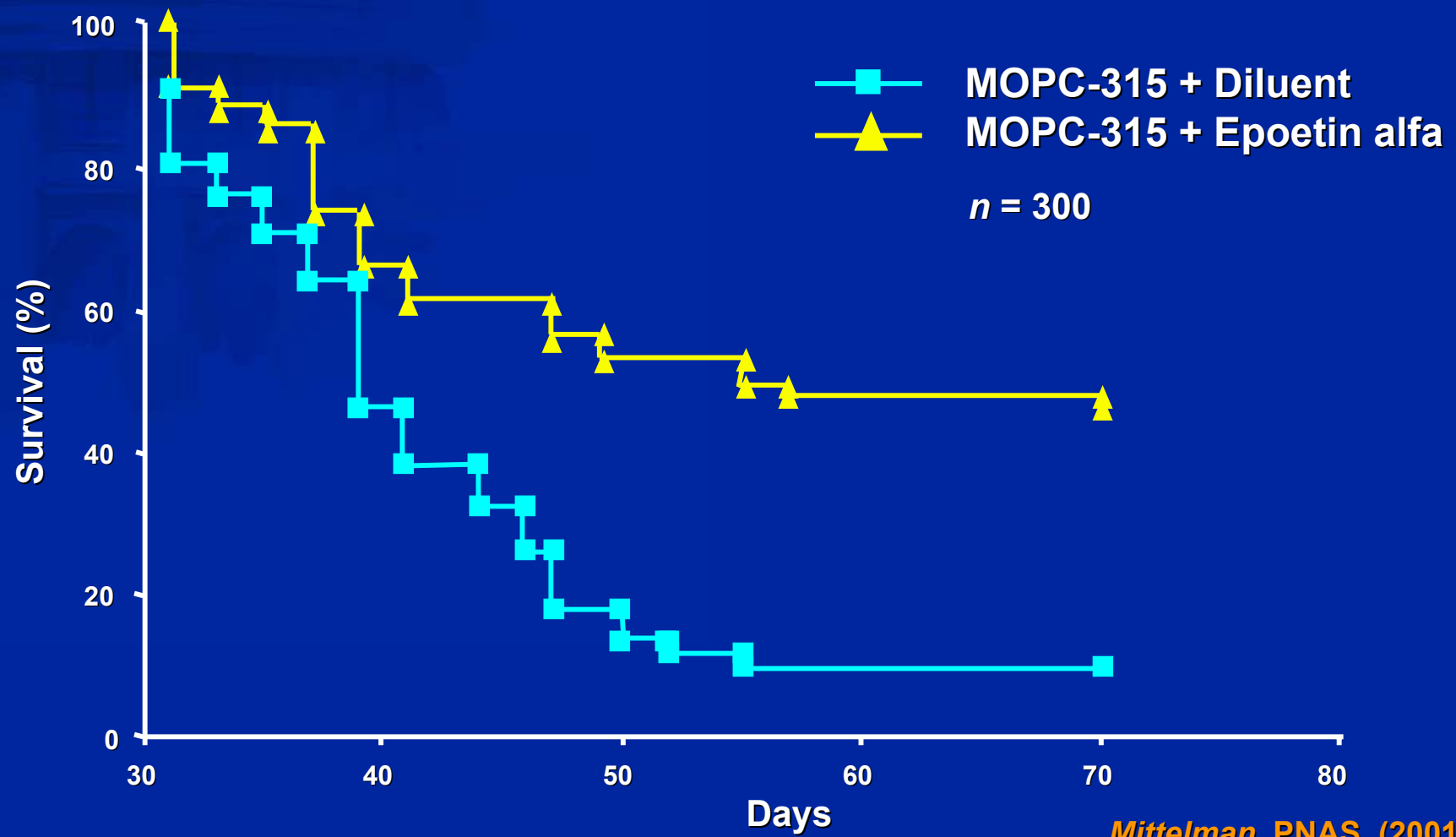
Mice Injected with MOPC-315



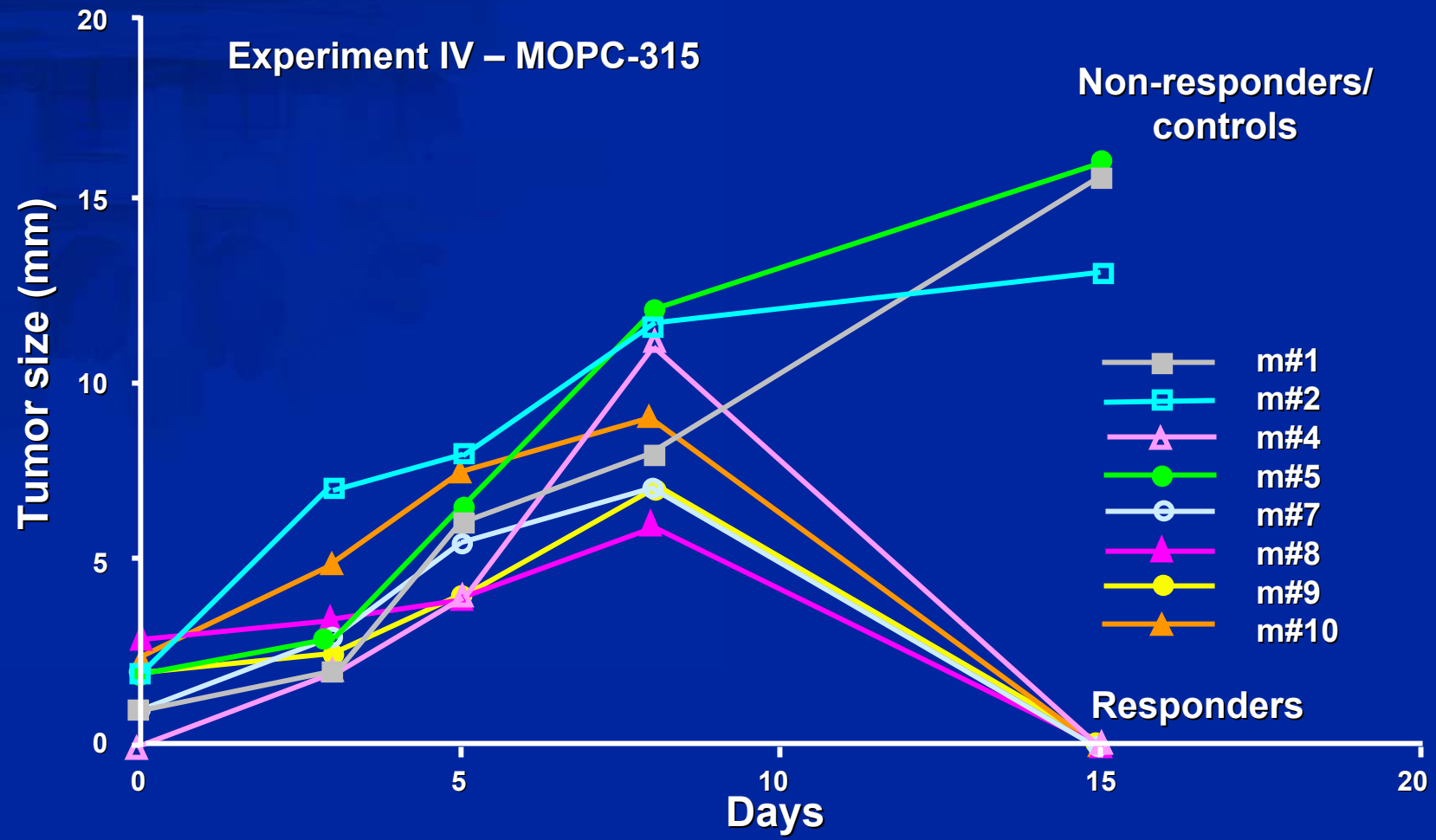
**Tumor
disappears**

Tumor

Survival Curves



Tumor Regression

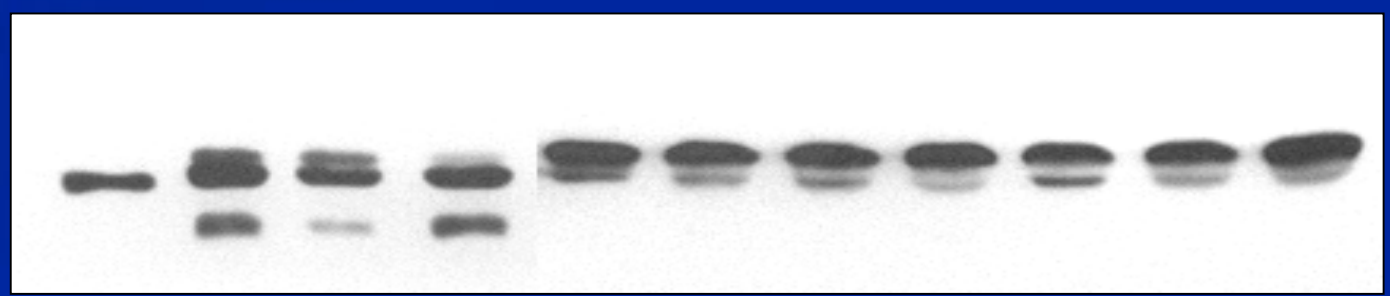


Protein Profile

M-Protein

Western blot

Polyclonal
globulins
M-Protein



1 2 3 4 5 6 7 8 9 10 11

MOPC
Ig

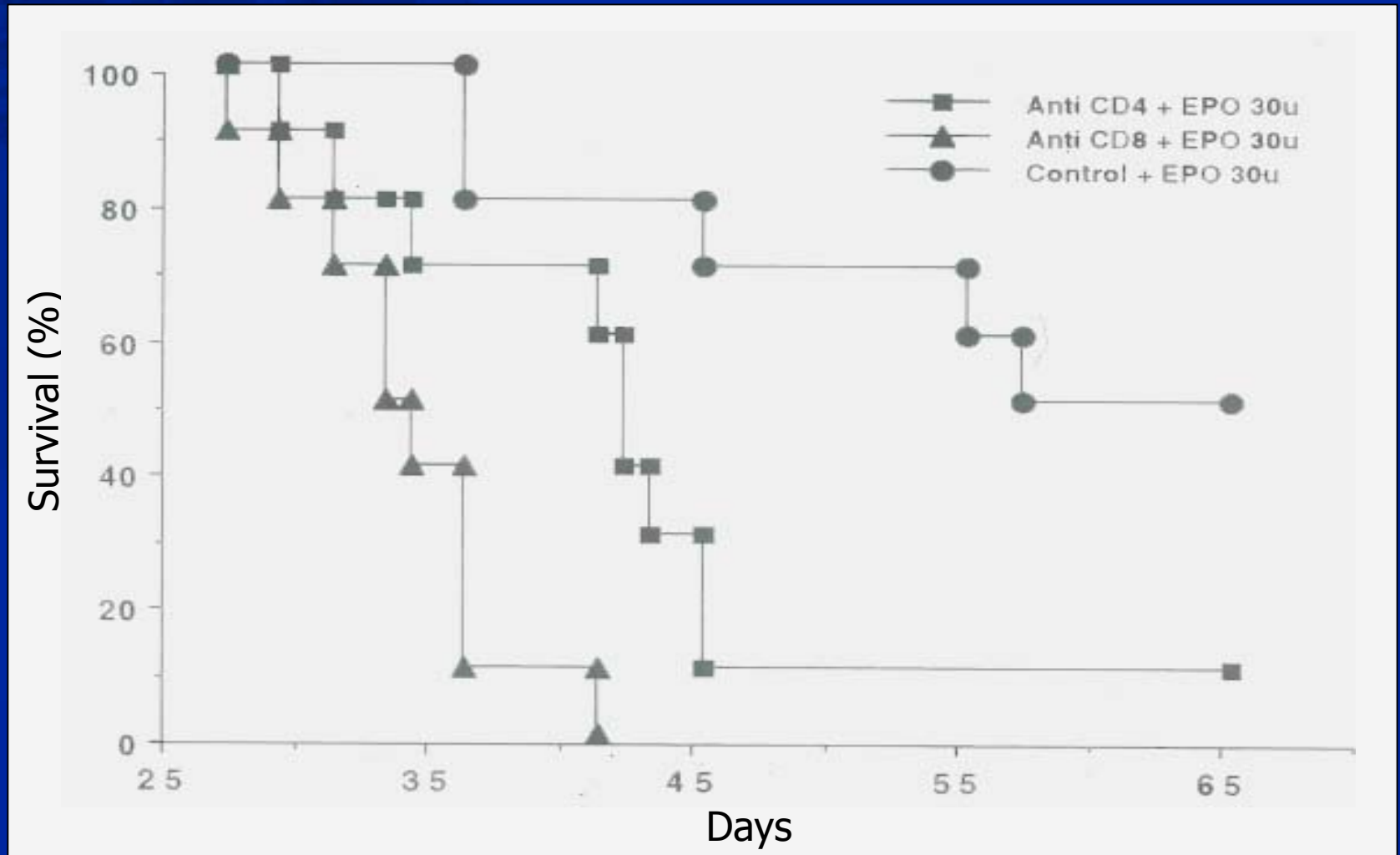
Progressors

Regressors (2 months)

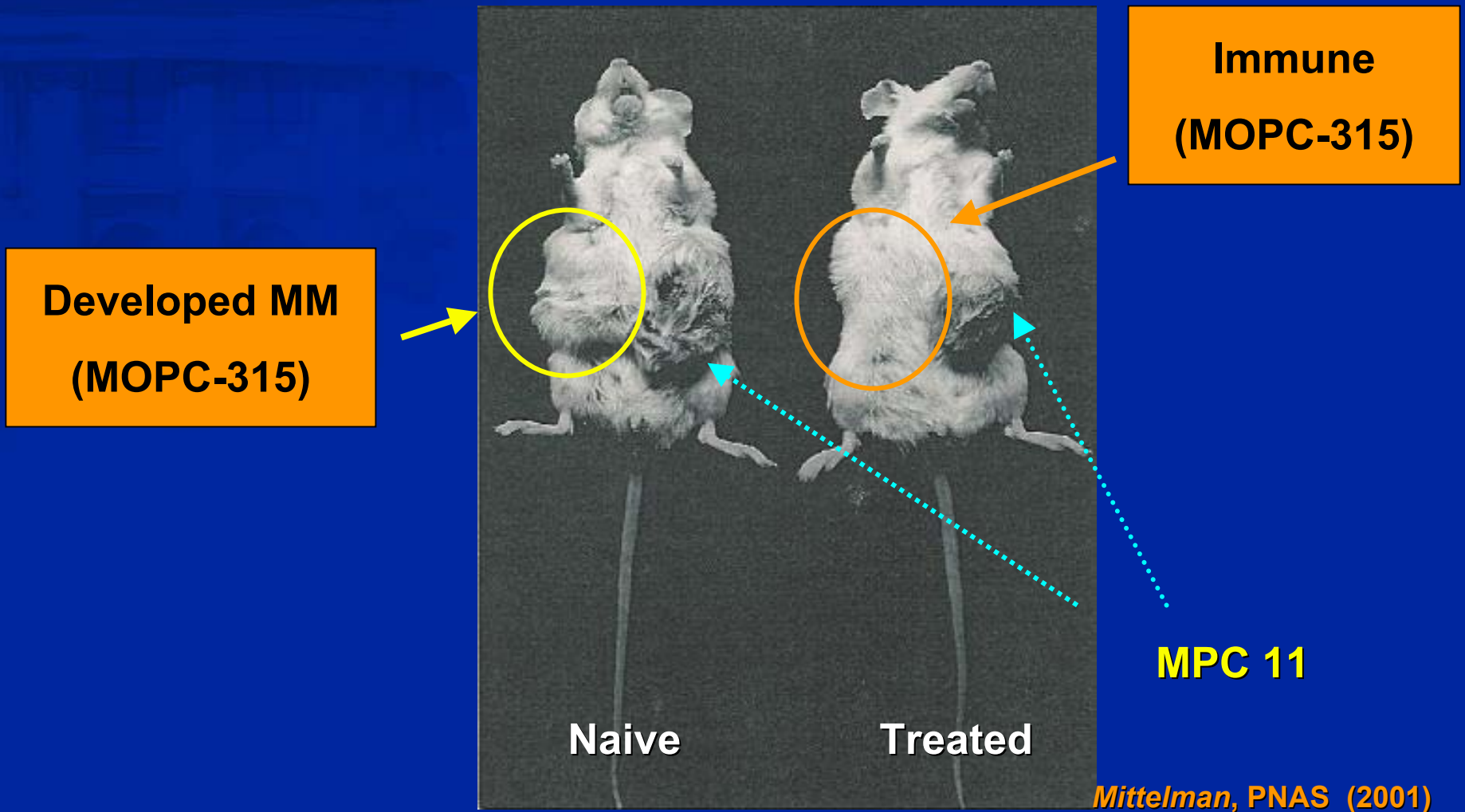
rHuEPO: Immunologic Mechanism

- rHuEPO in MOPC-BALB/c: **50% (mean) regression**
- EPO-R binding assay: **no receptor binding activity**
- rHuEPO in vitro: **no effect (conclusion: indirect!)**
- rHuEPO in SCID (and nude): **no effect!**
- rHuEPO + anti-CD8: **no effect (with anti CD4: partial)**
- Adoptive transfer: **Reg T-cells - tumor rejection**
- Winn Test: mixed tumor+Reg T: **tumor (1/10)**
(# all in others)
- Rechallenge

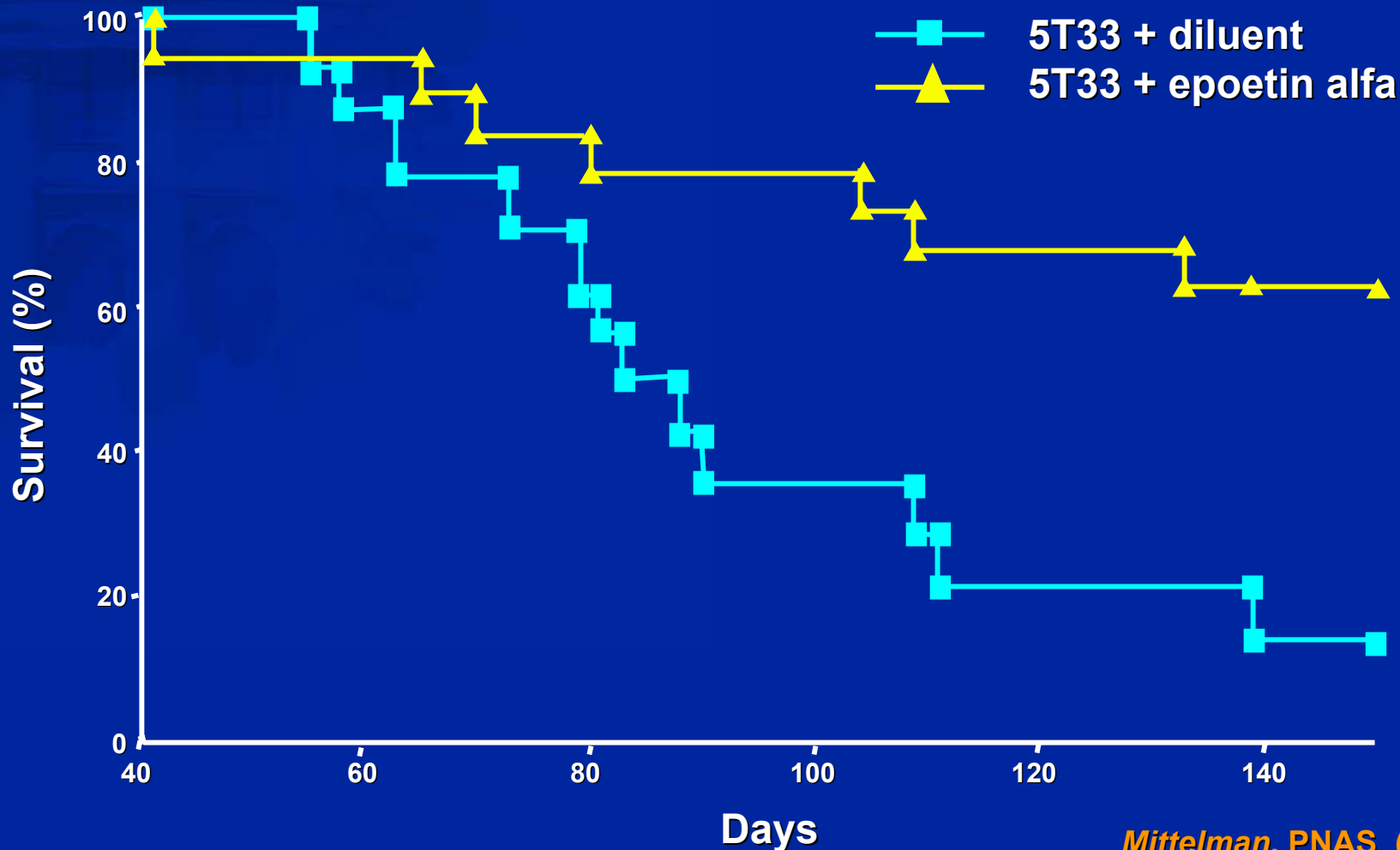
EPO: CD4/8 Neutralized



Rechallenge in Regressor and Naive Animals With Two Tumors



Survival in Other Models: 5T33 in C57BL Mice



rHuEPO: Antineoplastic effect

Literature

- **Ludwig, 1993: Responders live longer**
- **Rubins, 1995: RCC patient – regression**
- **Morere, 1997: 2/20 RCC patients**
- **Littlewood, 2001: Longer survival?**
- **Radiation is more effective – better prognosis**
- **Pangalis, 2002: Downstage CLL**
- **Wallvik, 2002: MDS patients on rHuEPO live longer**

rHuEPO: Nonerythroid Effects

- EPO receptors on many cells
- *Swirsky*: Immune functions of WBCs enhanced
- *Silverberg, 2001*: Improved CHF
- More effective radiation therapy
- *Cerami, 2001*: Neuroprotective
- *Grimm, 2002*: Prevents macular degeneration?
- *Sigounas, 2001*: Prevents lung fibrosis

Proposed Clinical Trial of Epoetin Alfa

- Phase 2 trial (706-001) in MM
 - 6 centers
- Major endpoint: survival
- Surrogate markers: M protein, cytokines, Igs, lymphocytes
- Novel dose regimen